

# IOWA STATE UNIVERSITY

## Digital Repository

---

Creative Components

Iowa State University Capstones, Theses and  
Dissertations

---

Spring 2020

## Immune Regulation and Helminth Therapy

Jeffrey Horak

Follow this and additional works at: <https://lib.dr.iastate.edu/creativecomponents>



Part of the [Alternative and Complementary Medicine Commons](#), [Digestive System Diseases Commons](#), [Immune System Diseases Commons](#), and the [Parasitic Diseases Commons](#)

---

### Recommended Citation

Horak, Jeffrey, "Immune Regulation and Helminth Therapy" (2020). *Creative Components*. 512.  
<https://lib.dr.iastate.edu/creativecomponents/512>

This Creative Component is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Creative Components by an authorized administrator of Iowa State University Digital Repository. For more information, please contact [digirep@iastate.edu](mailto:digirep@iastate.edu).

## **Creative Component**

### **Abstract:**

Parasitic helminth infections are highly prevalent worldwide, however the distribution of infections shows they are much more prevalent in developing countries. The distribution of Inflammatory Bowel Diseases (IBD) and allergies shows that they are inversely related to parasitic infections; countries with high burden of parasitic helminth infection show fewer cases of IBDs and allergies. This review examines a potential causal link between higher parasitic helminth infection and lower incidence of IBD and allergies. The focus will be the characteristics of a type 2 immune response and the interactions between a parasite and host upon infection (these two pathologies have many overlapping features and the regulation of the parasite within the host can have effects on the type 2 response), and the interaction of a type 2 response with IBD and allergies. Furthermore, current research that shows the gross applications of these interactions to IBD and allergy treatment, and the current direction of the field, will be discussed.

### **Introduction:**

Helminth infections are highly prevalent in our world with global reports estimating nearly one-third of the global population playing host to a helminth infection (1). This ranks helminths as one of the most prevalent groups of infectious agents in the world. Along with infection come many side effects that can be potentially dangerous. Helminth infections have been prevalent in humans for such a long time that, not only have the parasites themselves developed resistance to immune expulsion, but humans have also evolved to limit the effects felt by helminth infections. These coevolutionary events have

led to a symbiotic relationship where the host manages the symptoms, and does not expel the parasite due to the risk of greater injury.

This relationship has led to some interesting correlations showing how, when it comes to certain conditions like allergies and Irritable Bowel Syndrome (including Crohn's Disease and Ulcerative Colitis) the presence of a parasite in the host can have a beneficial effect. It has been shown that infection with parasites, such as helminths, can greatly reduce the symptoms related to these conditions. However, persistent helminth infections are not a suitable treatment option, due to their unpredictability and side effects.

Ultimately, the goal would be to mimic the presence of a parasite in the body, instead of actually treating the patient with a parasite. In order to mimic the effects we need to study the mechanisms, present in parasite infection, that give rise to its beneficial effect. If we are able to discover the specific proteins, cytokines, or mediators that provide a beneficial effect, and deliver them directly to the host, that would be an ideal therapy for these diseases.

To understand potential therapeutic agents, we first must understand the relationship between the parasite and the host. The mutually beneficial immunosuppressive type 2 immune response dominates during parasitic helminth infection and whilst it is well established that parasitic helminths contribute to driving this type 2 response, the exact molecular mechanisms used by the parasites to manipulate the host immune response are not well understood. A clearer appreciation of the host-parasite interface is required before we can therapeutically exploit helminths or their modulatory molecules as a treatment for conditions such as allergies and IBD.

**Type 2 Immune Response:**

Allergies and certain chronic diseases can be a result of inappropriate type 2 immune responses, and by over-reaction of the host due to sensitization. Typical type 2 responses have specific mediators and characteristic changes that occurs. The most common type 2 mediators are cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13. Other common characteristics are eosinophilia, mast cell activation, goblet cell proliferation, increased secretions, and elevated levels of reactive immunoglobulin (Ig)E.

The cardinal sign of a type 2 response is the presence of Th2 cells, which are the key modulators of the whole response. Once initially stimulated by IL-4, Th2 cells are induced from naïve CD4<sup>+</sup> cells. Th2 cells then help to orchestrate the entire type 2 response by secreting more IL-4 as well as IL-5 and IL-13. Th2 also facilitates B cell class switching, to produce IgE antibodies. Th2 cells also play a role in the progression of all of the other changes that occur with a type 2 response. Without Th2 cells, there would be no type 2 immune response.

IL-4 has two main effects, initially it helps to recruit more naïve CD4<sup>+</sup> cells to become Th2 cells, and later it is the main inducer of antibody isotope switching to IgE. IL-5 and IL-9 are important for the recruitment and activation of eosinophils and mast cells. IL-13 is responsible for goblet cell hyperplasia and for the elevated levels of secretions and hyper-responsiveness. These are the main cytokines in the type 2 response, although there are many others that play roles in the immune system, these are the most understood for type 2 immune responses.

Eosinophilia is an elevation in the number of eosinophils in the tissues and blood stream, typically eosinophilia is determined when the eosinophil count is greater than 450-550 cells/microliter. Eosinophils are important cells in the type 2 response, hence why there is an elevation upon parasitic infection. They are responsible for inducing inflammation upon release of their granules. Overactivation of eosinophils can lead to uncontrolled inflammation and potentially chronic inflammation. Historically eosinophils were only thought to be part of the late stage of a type 2 response, in which they are used in the fight against the parasite. However, recent studies have shown that eosinophils are present in the early stages of a type 2 response, and also have inducing effects for the type 2 response. It has been found that eosinophils produce IL-4, IL-6 and IL-13 early in the development of a type 2 response. The activation of Th2 cells by eosinophils is a good example of the interconnectivity between the innate and adaptive immune systems, and help explain the response to Th2 antigens, even in the absence of adaptive immune cells. (15,16)

Mast Cells are important cells for the late stages of a type 2 response, releasing their histamine containing granules to promote an inflammatory response. In cases of repeated type 2 antigen exposure, mast cell hyperplasia is seen. Bone marrow derived mast cell progenitors circulate and in the case of mast cell hyperplasia, more of these progenitors mature to form mast cells. Certain growth factors play a role in the increasing number of mast cells, but it has been found that a key component of this process is the influence of cytokines, specifically IL-3 and IL-4.

The increased levels of IL-13 during a type 2 response can promote goblet cell proliferation and hyperplasia. Goblet cells are secretory cells that help produce mucus

in the airways and parts of the GI tract. Goblet cells are typically a host defense cell that secretes mucus due to a number of stimuli, including inflammation. With normal levels, goblet cells are protective, but in the case of some type 2 responses, the increased IL-13 can lead to goblet cell proliferation and hyperplasia, which if stimulated can lead to excess mucus which can block the airways. This is commonly seen in asthma and some allergic reactions, the airways constrict and with the excess mucus release, the airways become blocked, this can be fatal in some cases. However, in the GI tract, the excess mucus can provide a beneficial function, providing an extra layer of protection in times of inflammation. (18)

The final key characteristic in type 2 responses is the switching to IgE antibodies. IgE isotypes are typically only seen in the presence of allergic reactions or in parasite infections. IgE isotypes can activate mast cells to release their granules, but in some cases, this overactivation of mast cells can lead to a drop in blood pressure due to the vasodilator histamine. If excessive, this drop in blood pressure can lead to anaphylactic shock.

All of these responses occur in a typical type 2 response, and it is easy to see how, when these are uncontrolled or inappropriate, they can be damaging to the host. In moderation type 2 responses can be beneficial to the host but with certain diseases repeated responses can have detrimental effects.

### **Helminth Infections:**

Helminth infections are typically labeled as a type 2 immune response, sharing many of the characteristics listed previously. What makes helminth infections different is that along with the type 2 response they also stimulate an immune regulatory network, which modulates an environment that promotes parasite survival without host expulsion (27). Helminths manipulate the host to create an environment that favors their survival, while limiting their detrimental effects. Some key components in the adaptive helminth response are the anti-inflammatory cytokines IL-10 and TGF- $\beta$ . Important cells for this response are Dendritic cells, alternatively activated macrophages, and T and B Regulatory cells. Collectively, these cells help to modulate the interactions between the

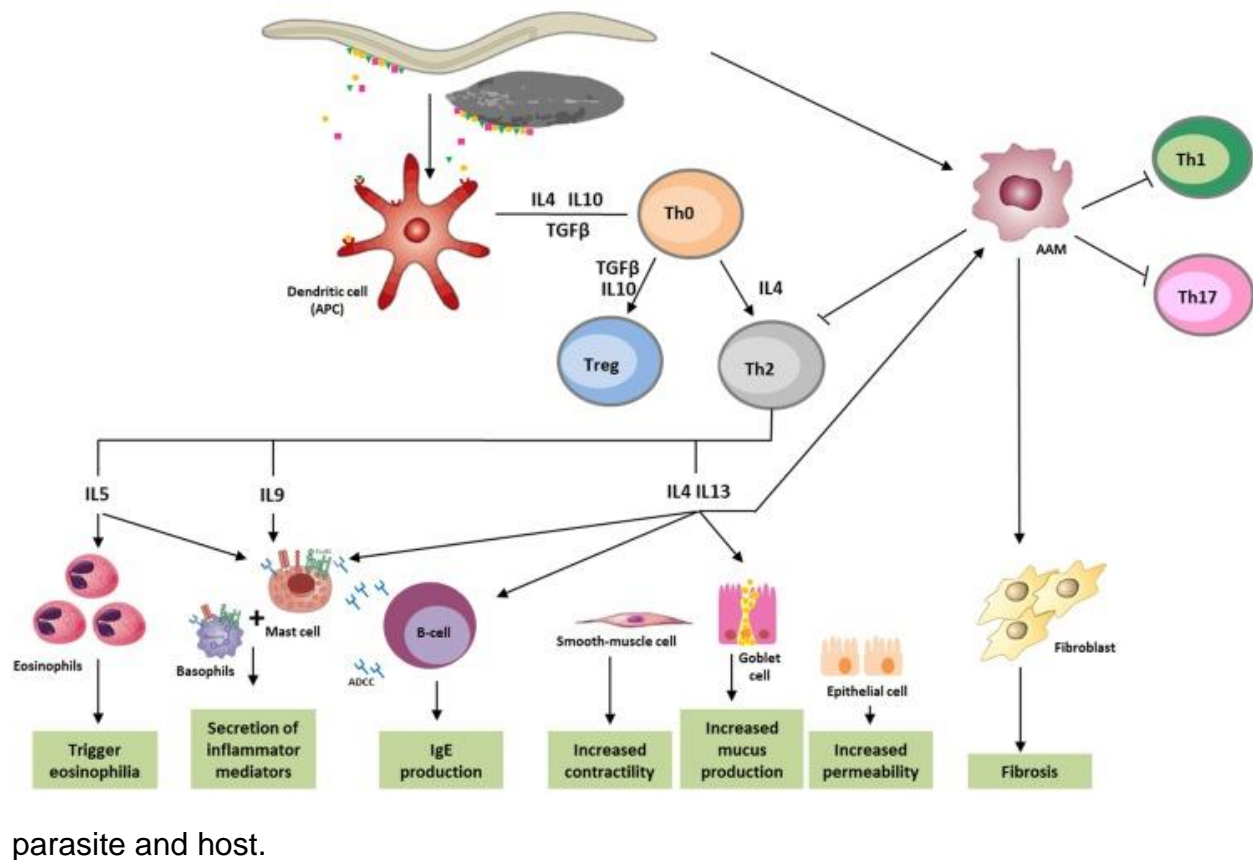


Figure 1: Immune response to helminth infection triggers many changes. Th2 cells  
<https://www.researchgate.net/figure/Immune-response-against-helminths-Helminth-infection-mainly-leads-to-Th2-mediated-many-cellular-changes>

IL-10 is a key anti-inflammatory cytokine that has been shown to have an immunosuppressive effect in both type 1 and type 2 immune responses. In type 1 responses IL-10 is key in limiting the effects of Th1 and CD8<sup>+</sup> cells which can be damaging if they are not regulated. In a murine study, it has been shown that mice devoid of IL-10 will succumb to lethal immune response due to overproduction of certain cytokines, that in moderate amounts have beneficial effects. In the case of helminth infections, IL-10 is upregulated, which helps to reduce inflammation and suppress the immune system. Parasites have adapted to the host, by ensuring the production of IL-10 to keep the immune system at bay, to prevent their elimination or expulsion.

TGF- $\beta$  proteins belong to a large superfamily, that can have many different effects depending on the environment, receptors, and isoforms. TGF- $\beta$  generally has an immunosuppressive effect, but it also serves many other functions. (8) TGF- $\beta$  is an important mediator in many pathways that lead to the overall type 2 response. It also induces the maturation of T cells into Tregs. Others functions of TGF- $\beta$  are still being explored as well.

Dendritic cells play an important role in the stimulation and modulation of the immune system in helminth infections. Known as the professional antigen presenting cells, dendritic cells present T cells with parasite derived antigens, driving Th2 cell activation. In a study where dendritic cells were depleted, the type 2 immune response was not present after helminth infection (9). This shows that dendritic cells are a critical component in the parasite host interaction. Although there is a better understanding of how dendritic cells interact with type 1 responses, it is clear that they have a primary role in the type 2 response as well, however the specific pathway and mechanism have



not been defined. Dendritic cells have a magnitude of receptors and so far, many different receptors have been shown to play a role in the induction of pro-regulatory dendritic cells. What is known is that when dendritic cells are induced to the pro-regulatory form, they act to promote type 1 regulatory (Tr1) cells, which produce the anti-inflammatory cytokine, IL-10. (1)

Alternatively activated macrophages (AAMs) are another key component of the helminth induced type 2 response. Differences in surface molecules and receptors are a main distinction between traditional macrophages and alternatively activated macrophages. AAMs are present in the type 2 response, and high levels have been detected in cases of helminth infection. Unlike traditional macrophages, AAMs have a suppressive effect on the immune system, modulated through anti-inflammatory agents such as IL-10, TGF- $\beta$ , PD-L1 and PD-L2. Specific subtypes of AAMs have been identified but those specific to helminth infections are shown to be induced by IL-4 and IL-13. There has been some complications in trying to replicate the *in vitro* response to an *in vivo* response. However, what has been determined is that AAMs do increase IL-10 production, whether this is a direct or indirect process is still up for debate. (11)

Regulatory T cells (Tregs) are critical to the permissive host immune response during parasite infection. Tregs are cells that typically control the immune response to self and some foreign antigens to prevent an autoimmune response. They act on other immune cells to suppress their activity in the presence of self antigens. After helminth infection, Treg populations expand as they are required for the long-term tolerance to the parasite. Tregs help control granuloma size in certain gut cells, and a reduction in granuloma size, means less inflammation when released. When Tregs numbers are

diminished by certain antibodies, an increase in granuloma size is seen (11). Much like we have seen before Tregs also produce IL-10, giving rise to the dampening of the inflammatory response. Tregs can be induced through the TGF- $\beta$  pathway, interestingly it has been shown that inhibition of the TGF- $\beta$  receptor, inhibits the induction of Tregs and parasites are expelled or in cases of chronic infection, the Type 2 response is increased (1). This shows the importance of Tregs in developing a symbiotic relationship with the host, and the importance of TGF- $\beta$  in the response.

Regulatory B Cells (Bregs), although not as essential as Tregs, also play a role in the helminth induced type 2 immune response. Although B cells are typically known for antibody production, which typically leads to an increase in inflammation, some specific B cells present in helminth infections have suppressive effects. B10 cells or Bregs have experimentally been shown to be produced following certain parasite infections. Bregs are yet another source of IL-10 and also can produce IgG1 antibodies which can suppress granulomatous responses during chronic infections. (12)

### **Type 2 Immune Pathologies :**

Inflammatory bowel diseases like ulcerative colitis and Crohn's Disease are characterized by repeated bouts of inflammation in the gut resulting in symptoms like diarrhea, weight loss and even malnourishment from low levels of nutrient absorption. These conditions are currently being studied and the underlying mechanisms are still somewhat unclear. These diseases are often chronic for patients and the treatment options that exist require lifelong medication. Due to the underlying mechanisms being unclear some patients fail to respond to the current medications, or over time notice a decrease in their responsiveness to them. (13) Although the underlying mechanisms are

unclear, what is known about inflammatory bowel diseases is that something triggers an inflammatory immune response in the gut, decreasing nutrient absorption. It has been hypothesized that bacteria, viruses, or antigens lead to the inflammation, or that a combination of these causes it. There has been recent evidence of a genetic factor that could lead to the development of the disease. Another common theory is that it is an autoimmune reaction which triggers the inflammation. If untreated or uncontrolled, the repeated bouts of inflammation can raise the patient's susceptibility for colon cancer.

Allergies are a phenomenon where there is an intense type 2 response, resulting in varying levels of inflammation. The underlying mechanism with allergies is an inappropriate response to an allergen that typically is not harmful to the host. The symptoms arise from the response to the allergen, after a sensitization period. Common allergies like dust mites, and cat dander can cause low levels of respiratory inflammation and increased secretions. On the other end of the spectrum are some individuals whose response to tree nuts or insect venom lead to extreme inflammation and anaphylaxis. The allergen itself in normal cases has no effect on the host, but in these cases the host's immune response to them is damaging. Excessive cytokine release and degranulation typically lead to the pathologies present in allergies.

**Hygiene Hypothesis:**

The Hygiene Hypothesis is a phrase that has been derived from the collection of data showing correlations between the higher frequencies of allergies and some autoimmune diseases in well developed countries compared to developing countries. The improved standards of living have resulted in lower infection rates in children, while

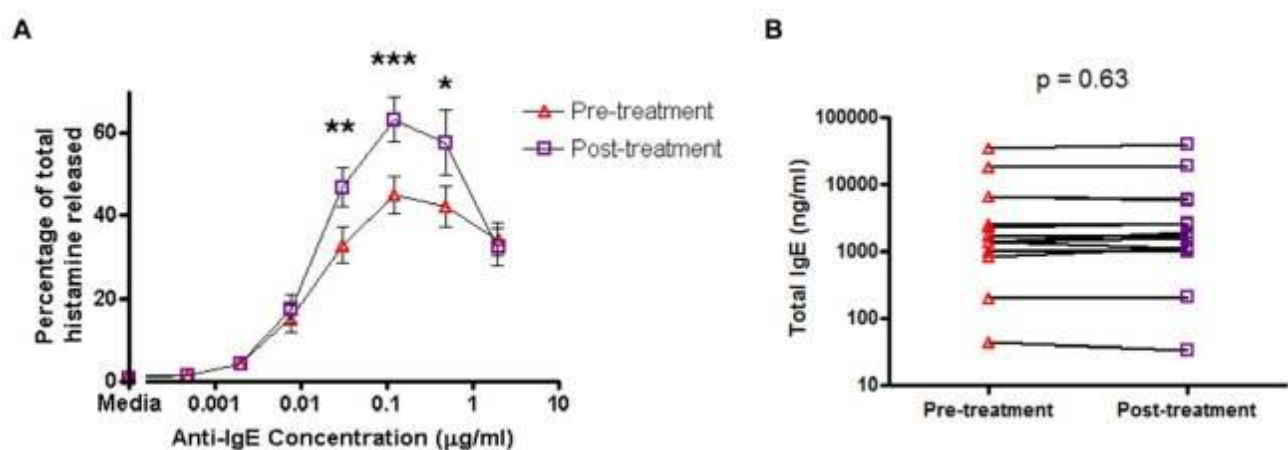
at the same time increasing immune dysregulation. (1) The overall cleanliness in developed countries has many positive benefits, and the lower infection rates decrease infant mortality rates. However, problems like allergies and autoimmune diseases are much more prevalent in the well-developed countries.

A lot of research interest has been focused on the role of helminth infections and the correlating decrease in allergies and autoimmune diseases. Under-developed countries have a significantly higher incidence of helminth infections compared to well-developed countries. Although it is not known what specifically ties these two phenomena together, there is positive correlation present. Allergies and autoimmune diseases are typically the result of auto-inflammation and the problems that arise when this is uncontrolled. Perhaps the symbiotic relationship of the parasite and host can provide a protective effect in the instance of these diseases. Most importantly, the anti-inflammatory effects of IL-10 and other mediators could suppress the effects of these auto-inflammatory diseases.

### **Helminth Therapy:**

In cases of overreactive type 2 responses, there is theoretical evidence that co-infection with a helminth parasite could lead to a suppression of the immune system, decreasing the severity and frequency of inflammatory bouts. In an indirect way the parasite's manipulation of the host not only ensures its own survival but could also diminish the effects of other type 2 immune pathologies. Studies have shown to have many positive effects on the regulation of inflammatory and autoimmune disease.

One early research study was done in a small community in Ecuador, in school-aged children who were previously infected with *Ascaris lumbricoides* and *Trichuris trichiura*. Serum samples were collected initially and again two weeks after an anthelmintic treatment was given. Researchers tested the responsiveness of the basophils collected in the serum samples. Results showed that the basophils collected two weeks after the anthelmintic treatment were significantly more responsive to stimuli and released more histamine than the basophils collected before treatment. IgE levels were also measured and no change was detected in the pre and post treatment serum samples. This study may be naïve in nature but the increase in basophil responsiveness confirms that the presence of the helminth infection suppresses the immune system. Additionally, it hints that the continued stimulation of the helminth infection may be needed to see beneficial effects. Although the underlying mechanism of what specifically causes the decreased responsiveness is not yet understood, this



gives a good macroscopic view of the potential benefits of helminth therapy.

Figure 2: Basophil histamine release in infected children before and 2 weeks after anthelmintic treatment. (A) Histamine release in response to increasing concentration of Anti-IgE (B) Total serum IgE levels pre and post treatment

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5387338/>

Although this first approach was novel, it still does not answer the question if helminths could be administered as a therapy. Another beneficial technique that arose was the administration of parasite eggs (ova) instead of infecting patients with whole parasites. *Trichuris suis* ova have been commonly used, and can elicit an immune response similar to a full parasitic infection. *T. suis* are parasites that infect pigs and are not pathogenic in humans. They are useful because they can partially stimulate the immune system while avoiding the risk of chronic infection. One downside with the ova administration is that they will not live and reproduce in the gut like traditional helminths would, so ova need to be administered every few weeks to maintain an adequate immune response. Additionally, ova can have significant side effects including diarrhea and GI disruption.

The first ova clinical trial was done with *Trichuris suis* ova and its effect on subjects with Crohn's Disease. (21) 29 patients suffering from Crohn's Disease were given 2,500 live *Trichuris suis* ova every 3 weeks for 24 weeks. Using detection methods specific for IBD's, it was shown that 23/29 (79.3%) of patients responded to the therapy, and 21/29 (72.4%) met the criteria for disease remission. Results were similar when tested at 12 weeks, suggesting that patients develop a response to the treatment prior to the full 24 weeks that was tested. This novel study has given rise to many similar clinical trials.

After the results of the *T. suis* studies, the question that needed to be addressed was what specifically caused the decrease in inflammatory cytokines, and the mechanism for this "treatment". These mechanisms were studied in animal models, and used a wide variety of parasites. *Heligmosomoides polygyrus* and *Schistosoma*

*mansoni* were two parasites that provided strong pathways and mechanisms for immune system suppression. *H. polygyrus* was studied in a murine model of IBD and its results were consistent with previous knowledge of disease protection, but furthered the details for the mode of action. Without parasite intervention, mice showed elevated levels of IL-12 and IFN- $\gamma$ , both of which are common inflammatory mediators. Upon *H. polygyrus* infection inflammation was reduced significantly, also IL-12 and IFN- $\gamma$  production was inhibited. What makes this research important was that it showed an IL-10 independent pathway for the suppression of inflammation. IL-10 is still a very important factor, but this shows that it is not the only way helminths suppress the immune system. T cells were transferred to an IBD mouse from both a *H. polygyrus* host and a control host. Only the T cells from the host infected with *H. polygyrus* showed immunosuppressive effects. These mice had their IL-10 production knocked out, so the only variable was the source of the T cells. Upregulation of Foxp3 mRNA expression was shown to be present in the T cells from the helminth infected mouse only, and is responsible for the regulatory activity of the T cells. (22)

Research into the mechanisms of immune regulation have led to the discovery of the importance of Foxp3<sup>+</sup> Regulatory T cells. Upon helminth infection, T cells are induced to express Foxp3, which gives them their specific regulatory functions. Foxp3<sup>+</sup> T cells are one of the major factors for immune suppression after helminth infection. More recently a specific receptor, IL-4 Receptor alpha, has been shown to be essential in the differentiation into Foxp3<sup>+</sup> Tregs. Adequate and functional IL-4 receptor alphas are required for inflammation control during helminth infections. (24)

Another study looked at the specifics of *Fasciola hepatica* infection and the roles of IL-10 and TGF- $\beta$ . Infection of the parasite suppressed the Th1 and Th2 responses of the host. This suppression was lost in mice with an IL-10 defect. Infection with the parasite also showed a bystander suppression of IFN- $\gamma$  and IL-17. These are common mediators for inflammation in response to autoantigens. This suppression was still present in mice with the IL-10 defect, but the suppression was reversed in mice when TGF- $\beta$  was neutralized. This shows again that there is not one specific pathway the parasite uses to suppress immune function, but in fact that they have integrated along many fronts. (23)

Most recently researchers are focusing on the use of parasite-derived products and parasite secretory products to elicit the same type 2 response and suppression. The goal with this research is to identify which components of the parasite interact with the host, and induce the immune response. Perhaps there is a specific secretory product that parasites expel which the host recognizes and induces a response. Identification of a specific product could lead to the pharmacological production of the product and an artificial induction of the host immune suppression without the need for introducing potentially pathogenic parasite material into the patient.

In a study with *H. polygyrus*, researchers looked at the specific *H. polygyrus* excretory-secretory antigen (HES) and its effect on the host. This specific protein was shown to induce Foxp3<sup>+</sup> Tregs which had suppressive effects. More specifically HES ligated the TGF- $\beta$  receptor on T cells. When this receptor was knocked out, all inducing effects induced by HES were eliminated. HES did not promote the development of Th1 or Th2 reactions under any conditions. These findings indicate that HES specifically



may be responsible for the Foxp3<sup>+</sup> induction of T cells. (25) This makes HES a potential candidate to be used as a helminth therapy. Knowing the direct mechanism of action of inducing Foxp3<sup>+</sup> Tregs, outlines a direct pathway that can be manipulated.

Another interesting secretory protein is ES-62 from filarial nematodes. ES-62 is a protein that was found to have multiple inducing effects, across a wide range of cells including macrophages, dendritic cells, B-cells and mast cells. Upon complexing with TLR4, ES-62 results in the modulation of many signal transduction pathways. The net effect of these pathway modulations is the generation of the anti-inflammatory immune response. The multi functionality of the modulating protein makes it an interesting protein to study for the development of pharmaceuticals that can target these same signal transduction pathways. (26)

New excretory proteins are being studied in the hope of identifying a specific pathway that can be manipulated to lead to immune suppression for inflammatory diseases. When identified these can be produced by biopharmaceutical techniques and hopefully be used to prevent unwanted inflammation and inappropriate antigen stimulation. It is critical to understand the mechanism of action for the specific proteins that will be used, to avoid unwanted systemic effects.

In these clinical trials very low doses of parasites or parasite derived products are used to ensure the safety of the subject. This can have an effect on conclusions because it makes it very difficult to match a control group. Those who receive the helminth therapy will experience side effects, and the placebo group will not, so the double-blinded nature of the study is in question. As research moves forward, limiting these side effects will help lead to more conclusive studies.

**Conclusion:**

Over years of co-evolution it is clear that parasites have been able to manipulate their host's immune system to ensure their survival. This process is done on many fronts, and there is not one specific mechanism that controls the host regulation of the parasite. It is clear that the suppression of the host's immune system can have added benefits in the presence of auto-inflammatory diseases. These interactions are being studied in the hopes to isolate a specific protein or mediator that provides the beneficial effects on its own. Future efforts will hopefully lead to potential interventions for inflammatory diseases and other pathologies.

## References:

- (1) McSorley, H. J., & Maizels, R. M. (2012). Helminth infections and host immune regulation. *Clinical microbiology reviews*, 25(4), 585–608.
- (2) Lechner, C. J., Komander, K., Hegewald, J., Huang, X., Gantin, R. G., Soboslay, P. T., Agossou, A., Banla, M., & Köhler, C. (2013). Cytokine and chemokine responses to helminth and protozoan parasites and to fungus and mite allergens in neonates, children, adults, and the elderly. *Immunity & ageing : I & A*, 10(1), 29.
- (3) A. H. van den Biggelaar, R. van Ree, L. C. Rodrigues et al., “Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10,” *The Lancet*, vol. 356, no. 9243, pp. 1723–1727, 2000.
- (4) Couper, Kevin N., et al. “IL-10: The Master Regulator of Immunity to Infection.” *The Journal of Immunology*, American Association of Immunologists, 1 May 2008,
- (5) Larson, D., Cooper, P. J., Hübner, M. P., Reyes, J., Vaca, M., Chico, M., Kong, H. H., & Mitre, E. (2012). Helminth infection is associated with decreased basophil responsiveness in human beings. *The Journal of allergy and clinical immunology*, 130(1), 270–272.
- (6) Caminati, M., Pham, D., Bagnasco, D. et al. Type 2 immunity in asthma. *World Allergy Organ J* 11, 13 (2018).
- (7) Gazzinelli, R. T., M. Wysocka, S. Hieny, T. Scharton-Kersten, A. Cheever, R. Kuhn, W. Muller, G. Trinchieri, A. Sher. 1996. In the absence of endogenous IL-10, mice acutely infected with *Toxoplasma gondii* succumb to a lethal immune response dependent on CD4<sup>+</sup> T cells and accompanied by overproduction of IL-12, IFN- $\gamma$  and TNF- $\alpha$ . *J. Immunol.* 157: 798-805.
- (8) Chin D., Boyle G. M., Parsons P. G., Coman W. B. What is transforming growth factor-beta (TGF- $\beta$ )? *British Journal of Plastic Surgery*. 2004;57(3):215–221. doi: 10.1016/j.bjps.2003.12.012.
- (9) Carvalho L, et al. 2009. Mechanisms underlying helminth modulation of dendritic cell function. *Immunology* 126:28 –34.

- (10) Kreider, T., Anthony, R. M., Urban, J. F., Jr, & Gause, W. C. (2007). Alternatively activated macrophages in helminth infections. *Current opinion in immunology*, 19(4), 448–453.
- (11) Layland LE, Rad R, Wagner H, da Costa CU. 2007. Immunopathology in schistosomiasis is controlled by antigen-specific regulatory T cells primed in the presence of TLR2. *Eur. J. Immunol.* 37:2174 –2184.
- (12) FairfaxKC,etal.2012.IL-10Rblockadeduringchronicschistosomiasis mansonii results in the loss of B cells from the liver and the development of severe pulmonary disease. *PLoS Pathog.* 8:e1002490. doi:10.1371/ journal.ppat.1002490.
- (13) Hazel, K., & O'Connor, A. (2020). Emerging treatments for inflammatory bowel disease. *Therapeutic advances in chronic disease*, 11, 2040622319899297.
- (14) Kovalszki, A., & Weller, P. F. (2016). Eosinophilia. *Primary care*, 43(4), 607–617.
- (15) Spencer, L. A., & Weller, P. F. (2010). Eosinophils and Th2 immunity: contemporary insights. *Immunology and cell biology*, 88(3), 250–256.
- (16) Sabin EA, Pearce EJ. Early IL-4 production by non-CD4+ cells at the site of antigen deposition predicts the development of a T helper 2 cell response to *Schistosoma mansonii* eggs. *J Immunol.* 1995;155:4844–4853.
- (17) Bischoff SC, Sellge G. Mast cell hyperplasia: role of cytokines. *Int Arch Allergy Immunol.* 2002;127:118–122.
- (18) Rogers DF. Airway goblet cells: responsive and adaptable front-line defenders. *Eur Respir J* 1994;7:1690–1706.
- (19) Schnoeller C, et al. 2008. A helminth immunomodulator reduces allergic and inflammatory responses by induction of IL-10-producing macrophages. *J. Immunol.* 180:4265– 4272.
- (20) Grainger JR, et al. 2010. Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF- $\beta$  pathway. *J. Exp. Med.* 207:2331–2341.

- (21) Summers RW, et al. 2003. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *Am. J. Gastro- enterol.* 98:2034 –2041
- (22) Elliott DE, et al. 2004. *Heligmosomoides polygyrus* inhibits established colitis in IL-10-deficient mice. *Eur. J. Immunol.* 34:2690 –2698.
- (23) Walsh KP, Brady MT, Finlay CM, Boon L, Mills KHG. 2009. Infection with a helminth parasite attenuates autoimmunity through TGF- $\beta$ - mediated suppression of Th17 and Th1 responses. *J. Immunol.* 183: 1577–1586.
- (24) Abdel Aziz, N., Nono, J. K., Mpotje, T., & Brombacher, F. (2018). The Foxp3+ regulatory T-cell population requires IL-4R $\alpha$  signaling to control inflammation during helminth infections. *PLoS biology*, 16(10), e2005850.
- (25) Grainger, J. R., Smith, K. A., Hewitson, J. P., McSorley, H. J., Harcus, Y., Filbey, K. J., Finney, C. A., Greenwood, E. J., Knox, D. P., Wilson, M. S., Belkaid, Y., Rudensky, A. Y., & Maizels, R. M. (2010). Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF- $\beta$  pathway. *The Journal of experimental medicine*, 207(11), 2331–2341.
- (26) Harnett W, Harnett MM. 2009. Immunomodulatory activity and therapeutic potential of the filarial nematode secreted product, ES-62. *Adv. Exp. Med. Biol.* 666:88 – 94.
- (27) Resende, S. D., Magalhães, F. C., Rodrigues-Oliveira, J. L., Castro, V. N., Souza, C., Oliveira, E. J., Carneiro, M., Geiger, S. M., & Negrão-Corrêa, D. A. (2019). Modulation of Allergic Reactivity in Humans Is Dependent on *Schistosoma mansoni* Parasite Burden, Low Levels of IL-33 or TNF- $\alpha$  and High Levels of IL-10 in Serum. *Frontiers in immunology*, 9, 3158.